Rapid estimation of pharmacokinetic parameters can be achieved through a simple vector projection technique applied to DCE-MRI gadolinium uptake curves

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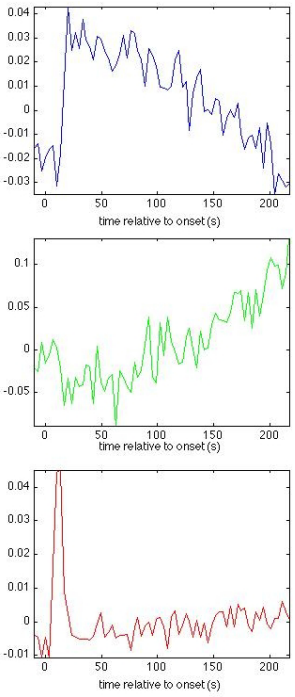

Figure 1 - Derived linear projections: K^{trans}(blue), v_e(green), v_p(red)

Introduction: Pharmacokinetic (PK) models can be fitted to dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) gadolinium (Gd) uptake curves in order to estimate PK parameters. In this work, a training set of Gd uptake curves (D_{test}), were fitted with PK models to produce a corresponding set of PK parameters (P). It is shown that using a cost fitting algorithm that is robust to outliers, a projection vector (b) can be derived for each PK parameter such that $D \times b = P$, where D is a matrix whose rows are uptake curves from each pixel, b is the projection vector and P is a vector of the chosen PK parameter for each pixel. This procedure essentially mimics the model fitting process as a simple linear projection. Outliers in the model fitted PK estimates mean that b cannot be optimised using a least squares methodology and so the 'robustfit' function from MATLAB® (Natick, MA) was used to optimise the linear projections. The projections obtained from the training set were then used on an independent test set, and correlations with model fitted parameters were assessed. This method of analysis is advantageous, as it does not require model fitting of any kind, is computationally efficient and requires no explicit AIF.

Methods: *Training set*: 126,478 Gd uptake curves was constructed from volumes of interest (VOI) in 11 patients with various tumours, each patient being imaged twice at baseline. Gd uptake curves for each voxel within a VOI were obtained using established protocols[1], each curve sampled at 3.3s intervals. Analysis of the uptake curves was conducted using MATLAB® (Natick, MA). Volume mean uptake curves were then visually inspected to find the nearest sample to onset and the data were temporally aligned, such that each curve consisted of 3 pre-onset samples and 67 post-onset samples. Extended Kety[2] models were fitted to the curves using a population AIF[3]. Hence PK parameter estimates were obtained for all cohort curves. *Test set:* A similar methodology, but with different sample intervals, was used to produce 278,900 curves and corresponding PK parameters from 13 patients, imaged twice pre and post treatment. These curves were then interpolated so they were sampled at the same intervals as the training set.
Training: For each PK parameter, K^{trans}, v_p, v_e; a 70 long vector (*Figure 1*), known as the *'b'* was produced that projected, as closely as possible, all the training set Gd curves into PK space, i.e. $D(126{,}478 \times 70) \times b(70 \times 1) \approx P(126{,}478 \times 1)$. The linear projections were optimised using Matlab®'s 'robustfit' function. *Testing:* A new PK estimate for each curve in the test set was then produced by multiplying each curve by the appropriate linear projection. The projection obtained PK parameters were then compared to those obtained through model fitting. Correlation coefficients between the model fitted and projected estimates were calculated on the entire dataset. A small proportion of outliers in the model fitting mean that the correlation coefficient can be misleading. Therefore correlation coefficients were also calculated on the 90% of data with the smallest discrepancies. For each visit, the mean PK parameter estimates across the VOI were calculated. Repeatability of each method was then assessed using a Bland Altman analysis[4].

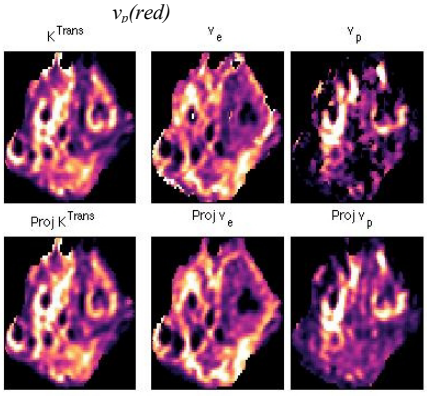

Figure 2 – Maps of PK parameters produced by model fitting and projection (proj) methods

Results: There was good correlation between the projection and model fitting methods: K^{trans} (r = 0.93, gradient = 1.18); v_e (r =0.82, gradient = 0.86); v_p(r =0.78, gradient = 0.73 For the 90% of estimates with the smallest discrepancies the correlations were: K^{trans} (r = 0.99, gradient = 1.09); v_e (r =0.97, gradient = 0.94); v_p(r =0.78, gradient = 0.73. The Bland Altman analysis (*Table 1*) shows better repeatability using the projection method. The computation time for projection of 278,900 curves into PK space for a given linear projection is around 0.5s on a desktop PC.

Discussion: *Figure 2* and calculated correlation coefficients show that linear projections can be derived from a training data set and then applied to a new dataset to produce PK estimates that correlate very well with model fitting techniques. This allows PK estimates to be obtained from a new dataset in a computationally trivial manner. *Table 1* demonstrates that the technique is of comparable repeatability with the established model fitting methods. Visual inspection of *Figure 2* shows that both methods produce very similar maps of K^{Trans} and v_e. Some visual differences are seen on the v_p map but model fitting of v_p is typically subject to larger errors[5]. The projection method is robust, may be applied to whole image datasets trivially and is not reliant on computationally expensive fitting algorithm. This method demonstrates the estimation of PK parameters is possible directly from the Gd curves through the application of linear projections and that the method is of better repeatability. Both datasets were obtained using similar DCE-MRI protocols so the generality of this method must be further investigated.

	Population mean (baseline)		Repeatability (baseline)	
PK Parameter	Model Fitting	Projection	Model Fitting	Projection
$K^{Trans}(min^{-1})$	0.161	0.139	0.086	0.060
v_e	0.237	0.204	0.085	0.070
v_p	0.009	0.010	0.003	0.003

Table 1 – Bland Altman analysis showing the repeatability of both methods

[1]Orton MR et al 2009 Phys. Med. Biol. 54 2197 [2]Kety SS, Pharmacol. Rev 3 1-41 [3]Parker GJM, Magn Reson Med 56(5) 993-100 [4]Bland, Altman International Journal of Nursing Studies 2010 47(8) 931-936 [5]Messiou C., et., al., *Proc. Intl. Soc. Mag. Reson. Med.* 19 (2011), 3143.

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